Hypertension after kidney transplantation
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CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

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Chapter 1

GENERAL INTRODUCTION

Kidney transplantation

Epidemiology and survival rates

Since the first kidney transplantation in 1950 and the introduction of robust immunosuppressive regimens in the 1970s, kidney transplantation has evolved as the most durable and quality of life improving renal replacement modality. Five-year survival probability for a kidney transplant recipient (KTR) is 86.8%, compared to 53% for a patient on dialysis (Figure 1a). The expected unadjusted remaining lifetime for a 40 year old patient on dialysis is 11.5 years, compared to 25.5 years of a transplant recipient (Figure 1b).

Successful transplantation results from various partially modifiable factors, including surgical techniques, donor characteristics and effective immunosuppression. Post-transplant complications involve predominantly manifestation of cardiovascular disease (CVD), allograft rejection, infections attributable to compromised immune status and development of malignancies.

Most kidney transplant recipients die with a functioning allograft, i.e. without returning to dialysis and the main cause of death of KTRs is of cardiovascular disease. But non-fatal cardiovascular disease is also highly prevalent in kidney transplant recipients (Figure 1c). Both fatal and non-fatal cardiovascular disease such as ischemic heart disease and stroke in KTRs are intertwined with transplant related factors such as allograft and donor characteristics and comorbid conditions.

Cardiovascular disease and hypertension after transplantation

Adult KTRs have an annual 50-fold increased risk for a cardiovascular event compared to the general population. In pediatric KTRs the risk of dying from a CVD event is also 40 times higher than in their healthy peers. CVD accounts for approximately 36% of deaths in kidney transplant recipients.

Hypertension and graft loss and mortality

There is convincing (i.e. grade Ia) evidence that blood pressure (BP) reduction substantially decreases the risk for CVD events and death including coronary events, stroke, heart failure and end stage renal disease (ESRD) in the general population. For KTRs no such level of evidence is available but observational data suggest that lowering blood pressure in hypertensive KTRs improves graft survival and lowers patients mortality. Landmark data from Opelz and colleagues show a strong association between BP and both graft and recipient survival (Figure 1d). Any 10 mmHg increase in systolic BP is associated with a risk of graft failure up to 15%. Also, patient survival rates are superior in patients without hypertension: each 10 mmHg rise in systolic blood pressure > 140 mmHg, is associated with a hazard ratio of 1.18 (95% CI 1.12 to 1.23) even after adjustment for allograft function.
These data also suggest that the damage to the allograft caused by prolonged elevated BP is partially reversible. Graft survival improved in patients with high systolic blood pressure (SBP) at 1 and 3 years and a normalised SBP (< 140 mmHg) at year 5, compared to patients who remained hypertensive in the 1st, 3rd and in the 5th year after transplantation. Lowering BP can provide significant benefits for graft and patient survival even several years after transplantation, which stresses the importance of BP control.18

Randomized controlled intervention studies in kidney transplant recipients that assess the effect of BP control, various BP targets or different antihypertensive regimens are scarce. Therefore, extrapolation of data from randomised trials on the effects of hypertension on CVD in chronic kidney disease (CKD), combined with data for large observational studies (KTR database cohorts) provides the rational for strict blood pressure control in the transplant population.15,18
Definitions of hypertension and blood pressure targets after kidney transplantation

Definition of hypertension and blood pressure targets

For the general population < 60 years, adults with diabetes as well as adults with non-diabetic chronic kidney disease, hypertension is defined as systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg. Blood pressure goals in adults > 60 years are < 150/90 mmHg.9,19 For children < 18 years, BP ≥ 95th percentile for gender, age and height is regarded as hypertension. For kidney transplant recipients, BP target is defined at < 130/80 mmHg by the guidelines of the Kidney Disease: Improving Global Outcomes (KDIGO) because they are classified in the high-risk for CVD. For children, guidelines vary between BP thresholds of p90 and p95.14,20,21

‘Resistant hypertension’ is the term to indicate failure to reach BP targets despite the use at minimum three different antihypertensive agents, including a diuretic.22 Although many patients seem to meet this condition, by far the most patients have secondary hypertension or are incompliant to medication or lifestyle changes.22-24 ‘Apparent resistant hypertension’ is therefore the preferred wording. Also, rare causes of secondary hypertension should not be overlooked: Figure 2 shows a rare but treatable cause of treatment resistant hypertension in a KTR.25

Diagnosis

Diagnosing hypertension using home BP measurement or ambulatory BP monitoring (ABPM) is preferred since reliance exclusively on office-based BP measurements would result in under- or overestimation of KTRs with hypertension.26-28 BP self-measurements can improve adherence. ABPM offers 24 hour registrations and is required when ‘white coat’ hypertension, drug resistance, symptomatic hypotension during antihypertensive therapy, or autonomic dysfunction is suspected.9

Nocturnal blood pressure

In the treatment of hypertension, nocturnal blood pressure is also of importance. Blood pressure falls with > 10% during night-time. However, as a result of altered circadian regulation, the absence of a nocturnal drop, so-called ‘non-dipping’, is common amongst ESRD and renal transplant patients.27,29,30 A non-dipping pattern is an additional, independent risk factor for CVD and all-cause mortality in essential hypertensives, ESRD patients and KTRs.27,31-34 In the long term, successful transplantation can significantly improve circadian BP profiles.35

Prevalence of post-transplant hypertension

Due to the heterogeneity in literature of definitions for hypertension in kidney transplant recipients, its true prevalence can only be estimated. Nevertheless, hypertension is observed in the majority of kidney transplant recipients and BP control rates are low. Overall prevalence in adults reaches up to 85%.16,26,37 Only 8% of patients treated with antihypertensive agents reached systolic target BP < 130 mmHg, although these data
are derived from research dated more than 20 years ago. Of the paediatric transplant recipients, approximately 60-70% meet hypertension criteria.

**Pathophysiology of hypertension after kidney transplantation**

Factors contributing to the pathophysiology of hypertension as well as traditional factors for hypertension are listed in Table 1. During the progression of CKD, nephrogenic factors, atherosclerosis and/or arteriosclerosis cause the increase in arterial stiffness and contribute to hypertension. The increased arterial stiffness is largely irreversible and although transplantation prevents progression, the KTR maintains this vascular status. The allograft factors and effects of immunosuppressive agents are additional contributing hypertension inducing factors in KTRs. Hypertension occurring in the peri-operative period is often caused by volume overload, delayed graft function and higher immunosuppressive dosages.
Donor factors

A recipient who has been transplanted with the kidney of a hypertensive donor is more likely to develop hypertension after transplantation, suggesting a genetic predisposition in the donor kidney. This theory of the primacy of the kidney is well shown by studies that observed remission of hypertension in patients after transplantation with a normotensive donor.

Immunosuppressive agents

After transplantation hypertension is attenuated by immunosuppressive regimens (Table 1). The corner stones of modern immunosuppressive regimens are corticosteroids and the calcineurin inhibitors (CNI) (i.e. cyclosporine and tacrolimus). Corticosteroids cause hypertension only by both increased renal sodium absorption and alterations in the vascular tone causing increased systemic vascular resistance.

Although CNIs are strong pharmacological agents preventing allograft rejection, paradoxically, exposure is associated with nephrotoxicity, which causes irreversible, progressive tubulo-interstitial fibrosis and glomerulosclerosis possibly via blood pressure and intra-renal hemodynamic effects. CNIs cause sodium retention and also reduce vasodilator nitric oxide and consequently alterations in vascular diameter and flow occur. These effects may promote the progression of hypertension. Besides the sodium dependency, effects on vascular tone and elevation of sympathetic nerve activity are involved in the pathogenesis of CNI induced hypertension. The more frequently prescribed tacrolimus has a more favourable side effect pattern than cyclosporine.

Sympathetic nerve activity

The renal sympathetic nervous system is thought to play an important role in blood pressure regulation. The tubules, juxtaglomerular apparatus and the vasculature are innervated by sympathetic nerves arising from the spinal cord in the ganglia T11 to L1. Postganglionic nerves cross the celiac and aorto-renal ganglia and reach the kidney through the walls of the extra- and intrarenal arteries. Elevated sympathetic nerve activity (SNA) induces changes in tubular sodium and water reabsorption, mediates renin-angiotensin-aldosterone system (RAAS) activation by the juxtaglomerular apparatus and adjusts glomerular filtration by vasoconstriction (Figure 3). Kidney failure is associated with a rise in SNA, manifested in early stages of CKD and is directly related to disease severity. Kidney transplantation itself has no deactivating effect on SNA. However, bilateral nephrectomy does decrease SNA. This suggests that a neural factor arising from the native kidneys is a centrally acting, hypertension inducing element. Kidney allografts are surgically fully denervated at the time of transplantation, but post-transplant nerve restoration is histological confirmed in both experimental and human studies. Reinnervation in time after transplantation is a continuous process, but whether nerve restoration after transplantation has beneficial or detrimental effects on graft function is yet unknown. Since overactive sympathetic drive may contribute to hypertension, (re)innervation of the kidney allograft could potentially contribute to progression of hypertension. Remarkably, renal sympathetic innervation in CKD has recently been
proposed as a supplementary factor causing renal fibrosis.\textsuperscript{68} The immunomodulatory capacities of SNA and the possible driving factor in low-grade inflammation open a new window on nephropathy and are subject of current research. A potential link between sympathetic driven neurotransmission and fibrotic, inflammatory processes was determined in mouse models with chronic kidney injury: innervated kidneys with CKD expressed more fibrosis than chemically denervated kidneys.\textsuperscript{68} These experimental data give ground to the idea that renal innervation could possibly contribute to progression of allograft nephropathy.

**Therapy for post-transplant hypertension**

To reach BP targets in kidney transplant recipients, a uniform management strategy is essential that consists of modifying lifestyle, adequate antihypertensive medication and therapy adherence.\textsuperscript{69} Previously, bilateral nephrectomy of the native kidneys was a last resort therapy for refractory hypertension in ESRD patients.\textsuperscript{70,71} However, over the last

<table>
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<tr>
<th>Transplantation related</th>
<th>Transplantation unrelated</th>
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<tr>
<td>Severe ischemia-reperfusion injury</td>
<td>Native kidney disease</td>
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<tr>
<td>Warm and Cold ischemia</td>
<td>Systemic sympathetic activity</td>
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<td>Delayed graft function</td>
<td>RAAS activation (by native kidneys, sodium intake, SNA)</td>
</tr>
<tr>
<td>Volume status: hypervolemic</td>
<td>Pre-existing hypertension &amp; left ventricular hypertrophy</td>
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<tr>
<td>Donor:</td>
<td>Primary hyperaldosteronism</td>
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<td>Sex (female &gt; male)</td>
<td>Vascular abnormalities causing renal hypoperfusion</td>
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<tr>
<td>Donor age</td>
<td>Traditional risk factors for hypertension:</td>
</tr>
<tr>
<td>Donor hypertension</td>
<td>Genetic predisposition to hypertension</td>
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<tr>
<td>Size of the kidney allograft</td>
<td>Sex (male &gt; female)</td>
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<tr>
<td>Genetic polymorphisms</td>
<td>Age</td>
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<tr>
<td>Impaired graft function mostly due to:</td>
<td>Obesity**</td>
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<td>Chronic allograft nephropathy</td>
<td>Hypercholesterolaemia</td>
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<tr>
<td>Thrombotic microangiopathy</td>
<td>Obstructive sleep apnoea syndrome (OSAS)</td>
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<td>Rejection*</td>
<td>High sodium – diet</td>
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<td>Recurrent / de novo kidney disease in graft</td>
<td>Smoking</td>
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<td>Graft artery stenosis</td>
<td>Alcohol intake</td>
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<td>Arteriovenous fistula after biopsy</td>
<td>Chronic psychological stress</td>
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<td>Obstructive uropathy with hydronephrosis</td>
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* acute, chronic, cellular or antibody mediated; ** may be transplant-related since BMI increases after transplantation
decades the procedure has been barely performed due to the risks and development of more potent antihypertensive drugs.\textsuperscript{16}

Pharmacological approaches are the current foundations of antihypertensive therapy. Dose modification or alteration of immunosuppressive drugs should also be considered at all times. Steroid avoidance reduces the need for antihypertensive drugs, without affecting risk of graft loss.\textsuperscript{72,73} Tacrolimus has less hypertension inducing effects than cyclosporine and conversion from cyclosporine to tacrolimus significant decreases BP.\textsuperscript{74-77} CNI-free regimens may be superior for amelioration of cardiovascular risk profiles, but currently they are only restricted for specific patient groups.\textsuperscript{78,79}

**Lifestyle**

Several life style interventions have been proven to be effective in the treatment of hypertension. These include: weight reduction (to ideal body weight), physical activity (30 min per day 5 times a week), cessation of smoking, sodium restriction (to 90 mmol/
day) and moderation of the use of alcohol (maximum of 2 alcohol containing drinks a day).\textsuperscript{80,81} Obesity adversely affects graft outcome. Weight loss is of special interest to KTRs because increase in body mass composition, especially body-fat, is a common finding after transplantation.\textsuperscript{82,83} Causal factors of weight gain in KTRs include physical and metabolic effects of restored kidney function and effects of corticosteroids on food intake.\textsuperscript{84} Low physical activity in KTRs is strongly associated with a higher CVD risk and all-cause mortality, stressing the necessity for physical activity.\textsuperscript{85} Sodium restriction needs to be an integrated part of each antihypertensive therapy. The KDIGO guideline on this aspect prescribes a target daily sodium excretion of < 90 mmol. However, 85% of Dutch kidney transplant recipients exceed this target with a daily urinary sodium excretion of 150-176 mmol/24 h.\textsuperscript{86-88}

**Pharmacology**

The choice of antihypertensive pharmacotherapy is based on co-morbidity, efficacy, tolerability and interactions with other drugs. Predominantly, the calcium channel blockers (CCB), beta- and alpha-1 blockers, angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blocker (ARB) are prescribed. CCBs are often first line therapy because they counteract vasoconstrictive effects of CNIs.\textsuperscript{89} Diuretics are beneficial since CNI induced hypertension is sodium dependent, however they are cautiously used.\textsuperscript{90,91} Although the use of ARBs and ACEi are controversial due to intrinsic effects of glomerular filtration rate that may mimic rejection, their use results in clinically significant reduction in proteinuria.\textsuperscript{92} The effects on graft or patient survival are unknown.\textsuperscript{93}

**Adherence to medication**

Low medication compliance, observed in of 30-50% of the KTRs, is a modifiable behavioural factor that negatively influences graft and patient survival.\textsuperscript{94-96} In adult KTRs, adherence to immunosuppressive agents is better than to non-immunosuppressive agents.\textsuperscript{97} Puberty as well as the transition from the small-scale, child-and-parent focused paediatric care at the age of 18, to a large-scale, adult care program can be accompanied with significant effects of non-compliance to medication regimens.\textsuperscript{98-100} Transition occurs in a period in which adolescents grow into young adults, increase their independency from parents and can experience less monitoring of their medical routine.\textsuperscript{101}

Adherence can be improved using fixed-combined agents and by limiting the frequency of medication-intake.\textsuperscript{102} Non-adherence rates falls from 79% with taking medications once daily to 51% with 4 times daily dosing.\textsuperscript{103} A cohesive transition program in which paediatric and adult healthcare services are integrated may improve compliance.\textsuperscript{104} Encouraging prescription of combination/fixed-dose antihypertensive agents may increase compliance and blood pressure regulation.\textsuperscript{101,105}

**Innovative hypertension therapies**

Because of the unmet needs for controlling BP as discussed above, over recent years innovative interventional strategies have been developed, while antihypertensive
pharmacological developments decline.\textsuperscript{106} As an advantage, interventional therapies omit medication adherence pitfalls. Furthermore, regulation for medical devices development has been more lenient than those for pharmacological agents, therefore the devices are easier launched.

Figure 4 provides an overview of recently developed antihypertensive intervention therapies. Electric stimulation of the baro-receptors, ‘baro-receptor activation therapy’, using an implantable device may lower BP (Figure 4a).\textsuperscript{107-109} Furthermore, in a selected group of patients, short term effects on BP reduction have been achieved using an mechanical implant in the carotid sinus that can enhance the baroreflex response and amplifies the blood pressure lowering response (Figure 4b).\textsuperscript{110-112} Also surgical ‘neurovascular decompression’ of looping arteries that compress rostral ventrolateral medullae, have shown to reduce BP in selected patients (not illustrated).\textsuperscript{113-116} Creating an arteriovenous fistula by implantation of an anastomosis device between the iliac artery and vein may reduce systemic vascular resistance and thereby reduces BP (Figure 4c).\textsuperscript{117,118} Importantly, most trials with innovative techniques are feasibility studies. Also it should be noted that the reported effects are mostly short-term (i.e. hours-days). The exciting positive open-label results create enthusiasm and quick developments lead to a rise in mainly small-scale, single centre studies. The Symplicity HTN-3 trial showed that sham-controlled as well as long-term follow-up confirmative studies are obligatory to further the role and learn the durability of the new technique and its long-term safety profile.

\textit{Renal sympathetic denervation}

In the first decade of this century, a catheter based technique for resistant hypertension was developed disrupting renal sympathetic nerves without affecting other innervation (Figure 4d).\textsuperscript{119} Renal sympathetic nerve denervation (RDN) is achieved percutaneously via the lumen of the renal artery, using a catheter connected to a radiofrequency generator. Renal sympathetic nerves in the artery wall are disrupted by applying a number of radio frequent ablations in a quadratic pattern up to 8 Watt, lasting for 120 seconds (Symplicity catheter). Since the proof of principle study in 2009 led to substantial BP reduction, RDN mushroomed as a treatment potential for resistant hypertension.\textsuperscript{120} Renal sympathetic nerve modification has been used long before pharmacological antihypertensive therapies were introduced. Radical surgical thoracic, abdominal and pelvic sympathetic denervation appeared a successful treatment for malignant hypertension. However, the high per-operative comorbidity, mortality and long-term complications replaced the technique by pharmacological agents.\textsuperscript{121} Observations from bilateral nephrectomy in transplant patients that resulted in a decrease of systemic sympathetic nerve activity, lower renin activity and BP, suggests that native kidneys contribute to hypertension possibly by both afferent and efferent neural factors (Figure 3). These observations founded the pathophysiological rationale for RDN in non-transplant therapy resistant hypertensive patients.

RDN has been proven in non-kidney-transplant patients with therapy resistant hypertension to be safe, even for kidney function. In two studies (Symplicity HTN-1
and HTN-2), a pronounced office based BP reduction of 22/11 to 32/12 mmHg was achieved after RDN, persisting for at least 6 months.\textsuperscript{120,122} These promising findings were countered by the Symplicity HTN-3 trial in which patients were randomized 2:1 to denervation or sham. The trial confirmed feasibility and safety of RDN but failed to demonstrate effects on systolic BP.\textsuperscript{123} In non-sham studies, patient and physician-related biases confounded in the positive results. Technical procedural and a large inter-individual variety in BP responses after RDN in Symplicity HTN-studies may be caused by incomplete nerve disruption.\textsuperscript{124}

Nowadays, the initial widespread enthusiasm fuelled by Symplicity HTN-1 and HTN-2 studies, has been tempered by the outcome of Symplicity HTN-3.\textsuperscript{125} At least the Symplicity HTN trials have highlighted the importance of confounding in hypertension research, the trial effects, the importance of correctly diagnosing treatment resistant hypertension and the importance of medication adherence verification. Native kidney denervation has a strong pathophysiological rationale in hypertensive renal transplant patients: it may decrease daily drug dose, thereby increasing adherence and following this one-time intervention and it is unlikely that the native kidney is harmed. Finally, the lowering of CVD risk can be of substantial benefit. A feasibility study in renal transplant recipients was designed in 2012 (Netherlands Trial Registry number 3866, Academic Medical Center, Amsterdam).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig4.png}
\caption{Innovative strategies to lower blood pressure. Figure 4a: Electric baro-receptor stimulation, Figure 4b: Mechanical baro-receptor stimulation, Figure 4c: Ileac arteriovenous fistulation, Figure 4d: Cathether-based renal sympathetic denervation.}
\end{figure}
Assessment of renal sympathetic nerve activity

To further our understanding of the pathogenesis of hypertension and the interplay of the kidney (either transplanted or not) and the autonomic nervous system, assessment of the human renal sympathetic nerves is essential. Assessment of renal sympathetic nerve activity in-vivo can only be performed using indirect methods. Norepinephrine spillover methods using radiotracer dilution is the gold standard method: regional venous sampling quantifies the norepinephrine released from the kidneys into the circulation. However, this method is invasive and the compound is not easily available in Europe.

\textbf{123I-mIBG scintigraphy}

We proposed the minimal-invasive renal 123Iodide-metaiodobenzylguanidine (123I-mIBG) scintigraphy to measure sympathetic nerve activity. In nuclear cardiology, 123I-mIBG is used to assess adrenergic integrity and functionality of nerves in myocardial tissue. Principally in heart failure patients, 123I-mIBG uptake and washout rates are routinely used as prognostic factors.\textsuperscript{126-129} mIBG is a chemical modification of the false-neurotransmitter guanethidine (a former anti-hypertensive agent and potent neuron blocking agent). Uptake pathways for norepinephrine into the presynaptic terminals take up guanethidine into the presynaptic terminals. When mIBG is labelled to 123-I, visualization of sympathetic nerve terminals containing 123I-mIBG is possible (Figure 5). The amount of uptake of 123I-mIBG reflects density and functional intactness of neural tissue within the organ, whereas washout, the rate at which the labelled mIBG is cleared from the synaptic cleft, reflects sympathetic activity. After heart transplantation, a progressive increase in myocardial uptake of 123I-mIBG is seen, proving reinnervation of the myocardium.\textsuperscript{130} The changes in sympathetic nerve activity after RDN have been assessed with cardiac 123I-mIBG scintigraphy.\textsuperscript{131}
OUTLINE OF THIS THESIS

Kidney transplant recipients are at a high risk for cardiovascular disease, for which hypertension is a prime modifiable risk factor.

**Chapter 2** evaluates prevalence of hypertension and treatment efficacy in Dutch kidney transplant recipients.

In **Chapter 3**, the epidemiology of hypertension after kidney transplantation is further elaborated in paediatric and young adult kidney transplant recipients. It provides an analysis of the effects of transition from the paediatric to adult nephrologic care on hypertension control.

Since lifestyle interventions are thought a paramount antihypertensive therapy but have hardly been studied in kidney transplant recipients, dietary restriction of sodium chloride on blood pressure reduction in kidney transplant recipients is studied in **Chapter 4**.

The absence of nocturnal dipping in blood pressure, an additional risk factor for cardiovascular disease, may be related to the immunosuppressive regimens in kidney transplant recipients. Therefore, we evaluated the prolonged release vs. twice daily calcineurin inhibitor tacrolimus in **Chapter 5**.

Since the sympathetic nervous system contributes to the pathophysiology of hypertension and the rationale for renal catheter-based denervation, interruption of the nerves is a possible treatment target. In order to assess the changes in renal sympathetic nerve activity, we studied the nuclear imaging technique $^{123}$I-mIBG scintigraphy in kidney transplant recipients.

In **Chapter 6**, this technique quantified reinnervation of renal sympathetic nerves in kidney allografts at various time periods after transplantation.

In **Chapter 7** we assessed the changes in renal sympathetic nerve activity after renal denervation using $^{123}$I-mIBG scintigraphy.

To conclude, we describa the case case of a kidney transplant recipient treated with renal denervation of his native kidneys for the treatment of resistant hypertension in **Chapter 8**.
Chapter 1

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